1.2. The requested priority statement has been supplied.

1.3. On October 1, 2002, the Examiner confirmed by phone that we could request that the drawing requirement be held in abeyance, and we so request. We are in the process of procuring the necessary fulltone photographic prints, and they will be filed in due course.

2. Statutory Subject Matter (OA §11)

2.1. Claim 5 has been amended to recite an isolated protein, as suggested by the Examiner. Claim 5 recites three different entities: (i) a protein derived from Chlamydia, (ii) a sequence variant of (i), and (iii) a subsequence of (i). Since the subsequence can be relatively small, we changed the preamble to recite "a protein or peptide". The first entity is necessarily an isolated protein. However, the other two may be isolated and/or non-naturally occurring, and this likewise is acknowledged by the preamble. In the case of (iii), "non-naturally occurring" refers to the subsequence as an independent molecule.

2.2. Claim 12 has been replaced by new claim 18, which recites specific process steps.

3. Enablement (OA §12)

The Examiner concedes enablement for the polypeptide of SEQ ID NO:2, but not for "variants and subsequences".

We have amended the claims to recite that the variants have a minimum amino acid sequence identity of 80% to the recited polypeptides. In this regard, it should be noted that the typical sequence identities among the recited polypeptides, which are of similar biological function, are in the range of 53%-66%. The Examiner has acknowledged that the "80%" limit is taught on page 10.

While the claims do not specify the particular amino acid positions at which mutation is allowed, or the replacement amino acids for each such position, we believe that these choices are reasonably left to those skilled in the art. In other words, it does not require undue experimentation to determine which positions are tolerant of mutation, and then to determine a replacement set for each.

Typically, the positions least tolerant of mutation are concentrated into a small portion of the protein, the "binding site". This is the portion of the protein which mediates its biological activity.

If several proteins with similar activity are known, the residues tolerant of mutation can often be identified by aligning the sequences and identifying the variable positions. In general, surface residues, other than those which are part of the binding site, are highly tolerant of mutation, and hence highly variable in families of homologous proteins. Hence, tolerant positions can be predicted by first categorizing the positions as surface or internal (based on hydrophilicity) and then identifying the binding site. The latter can be done by, e.g., testing fragments for activity.

Alternatively, a simple technique for rapidly identifying tolerant positions is alanine scanning mutagenesis, where a set of single substitution mutants is prepared by systematically replacing each non-alanine residue with alanine. The mutants are then tested to determine if they retain an acceptable percentage of the biological activity of the wild-type protein.

Once positions tolerant of mutation are identified, one can predict an allowed set of replacement amino acids by reference to the generally accepted concept of conservative substitution (e.g., Leu for Ile), which recognizes that in families of homologous proteins, certain exchanges occur more often than

chance can explain. Alternatively, different replacements can be tested. It has been shown that in general, substitutions are roughly additive in their effects, so the activity of a multiple substitution mutant can be inferred from the activities of the corresponding single substitution mutants. However, cooperative effects can be examined with combinatorial libraries, if desired.

We do not agree with the Examiner that the specification fails to provide any guidance. In comparing Omp 4-15, it identifies regions of more pronounced homology (P14, L29-31 and Figs. 8A-J), and calls special attention to the GGAI repeat, to the region 400-490 (especially the FYDPI), and to a W in the C-terminal region. See P14, L31-P15, L8. At page 10, line 16, it alludes to concept of "conservatively changed amino acid resides". Throughout the specification, there is recognition that fragments (subsequences) can have activity.

The claims now recite that the "variants" and "subsequences" must comprise at least one epitope of the native protein, so that they have immunological activity. If the variant is being used to elicit a cross-reactive response to the native protein, that retention of just one epitope is needed. Hence, the Van de Loo example is not apropos.

4. Definiteness Issues

4.1. Claim 5 now recites an "isolated" protein.

4.2. Claim 5 no longer recites "a similar biological function", referring instead to an epitope of the native protein.

4.3. The "variants" and "subsequences" of claims 5, 7, 10 and 12 have been limited, as previously discussed.

4.4. The limitation "such as a human" has been excised.

4.5. Claim 18, replacing 12, recites method steps.

4.6. Claims 5, 7, and 10 now use proper Markush group form.

5. Prior Art Issues

Claims 5, 7, 10 and 12 each stand rejected as anticipated by Melgosa et al. (OA §§14-17).

Melgosa et al. teach a single protein of 98-kDa from the outer membrane complex of *Chlamydia pneumoniae*. The last words of said reference states "further molecular and antigenic studies of the 98-kDa will help to understand the role of this protein in structure as well as pathogensis of *C. pneumoniae*". Thus, by studying Melgosa et al. a person skilled in the art would not have been lead to conclude that the gel band disclosed by Melgosa et al. in fact contained several different proteins. All the proteins of the infectious elementary bodies have now been published by the present inventors in Electrophoresis 2001, 22, 1204-1223, enclosed. In table 3 of said article a list of identified proteins from *C pneumoniae* based on MAILDI-TOF-MS is listed and several proteins show a M, within the detection limit of the 98 k-Da disclosed by Melgosa et al.

In face, the present invention is based upon further studies of "the" protein of Melgosa et al., cf. the description page 5, line 30-page 6, line 4. At that time further molecular and antigenic studies of the 98-kDa band were not readily possible e.g. any attempt to clone and obtain an amino acid sequence from a single protein from the 98-kDa band by Edman-degradation would not have been possible due to the "contamination" of the other proteins in the spot. Thus, the inventive step of the present invention relates to the discovery by the present inventors that the gel band did contain more that one protein and thus the cloning and sequencing of some of said novel proteins.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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Enclosure
-Vandahl, et al., "Proteome analysis of the Chlamydia pneumoniae elementary body", 22:1204-23 (2001)

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claim 12 has been deleted.

Claim 18 has been added.

Claims 5, 7, and 10 have been amended as follows:

5 (amended). A non-naturally occurring or isolated protein or peptide which is (i) an isolated protein derived from Chlamydia pneumoniae having the amino acid sequence selected from the group consisting of [shown in] SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and [or] SEQ ID NO:24, or (ii) a variant protein [or subsequence thereof] having an amino acid [a] sequence [similarity] identity of at least [50%] 80% to at least one of said isolated proteins, or (iii) a peptide or protein which consists of an amino acid sequence which is a subsequence of at least one of said isolated proteins, said variant protein or subsequence comprising at least one epitope of at least one of said isolated proteins [and a similar biological function].

7 (amended). A diagnostic kit for the diagnosis of infection of a mammal[, such as a human,] with Chlamydia pneumoniae, said kit comprising a peptide or protein [with the amino acid sequence SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, or SEQ ID NO:24, or a variant or subsequence thereof] of claim 5.

10 (amended). A composition for immunising a mammal[, such as a human,] against Chlamydia pneumoniae, said composition comprising a peptide or protein [with the amino acid sequence shown in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, or SEQ ID NO:24, or a variant or subsequence thereof] of claim 5.